Azathioprine Is Superior to Budesonide in Achieving and Maintaining Mucosal Healing and Histologic Remission in Steroid-dependent Crohn's Disease

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Background: The effects of azathioprine (AZA) and budesonide (BUD) on mucosal healing and histologic remission of Crohn's disease (CD) are insufficiently studied. In this prospective study we evaluated the comparative effects of AZA and BUD on endoscopic and histologic activity in patients with steroid-dependent Crohn's ileocolitis or proximal colitis who had achieved clinical remission on conventional steroids.

Methods: Patients were randomized to AZA (2.0–2.5 mg/kg a day) or BUD (6–9 mg a day) for 1 year. The study protocol included clinical examination, laboratory tests, calculation of the Crohn's Disease Activity Index (CDAI), completion of the Inflammatory Bowel Disease Questionnaire (IBDQ), at baseline and then every 2 months for 1 year. Ileocolonoscopy with regional biopsies was performed at baseline and then at the end of the study to assess mucosal healing and the histologic activity of CD.

Results: Thirty-eight patients were randomized to AZA and 39 to BUD. At the end of the study 32 and 25 patients in the AZA and BUD groups, respectively, were in clinical remission ($P = 0.07$). The Crohn's Disease Endoscopic Index of Severity (CDEIS) score fell significantly only in the AZA group ($P < 0.0001$). Complete or near complete healing was achieved in 83% of AZA-treated patients compared with only 24% of BUD-treated patients ($P < 0.0001$). Histologic activity as assessed by an average histology score (AHS) fell significantly only in the AZA group ($P < 0.001$ versus baseline) and was significantly lower than in the BUD group at the end of the study ($P < 0.001$). Eight patients in the AZA group were withdrawn for adverse events ($n = 6$) or relapse of disease compared with 14 patients in the BUD group who were withdrawn for relapse of disease.

Conclusions: In patients with steroid-dependent inflammatory Crohn's ileocolitis or proximal colitis who achieve clinical remission with conventional steroids, a 1-year treatment with AZA was superior to BUD in achieving and maintaining mucosal healing and histologic remission.

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Key Words: Crohn's disease, azathioprine, budesonide, mucosal healing, histologic remission

Crohn's disease (CD) is a lifelong idiopathic intestinal inflammatory disease characterized by a chronic relapsing or unremitting course that reduces health-related quality of life (QOL).[1,2] Corticosteroids are the first-line treatment for active CD but even after the first course a substantial proportion of patients become dependent or refractory to steroids.[3,4] The immunomodulators azathioprine (AZA), 6-mercaptopurine, and methotrexate may maintain remission of steroid-dependent CD.[5–9] More recently, anti-TNF (tumor necrosis factor) agents have proven highly efficacious in inducing and maintaining remission of steroid-dependent moderate-to-severe CD.[10–14] All these drugs may achieve mucosal healing to a certain degree.

The value of mucosal healing as a primary therapeutic target in CD is debatable. Mucosal healing is neither a prerequisite for clinical remission nor predictive of clinical relapses of CD, but it is undoubtedly desirable because it may be predictive of better disease outcome.[10–12] In an early GETAID study[15] steroids were shown to induce mucosal healing in less than one-third of patients with active CD; colonic lesions healed slowly but ileal lesions seemed to resist healing. However, steroids will not maintain remission and chronic exposure is associated with dangerous and potentially life-threatening complications.[16] Budesonide (BUD), a locally acting steroid, lacks many of the systemic effects of conventional steroids. BUD induces

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remission in mild-to-moderately active Crohn's ileocolitis,[17–19] helps taper conventional steroids and reduce steroid-related side effects,[20,21] and prolongs the period of remission compared to placebo and mesalamine.[22–24] Flexible dose regimens (3–9 mg a day) may maintain remission for 1 year.[25] However, the effects of BUD on mucosal healing have not been studied.

AZA allows maintenance of remission and weaning of steroids in approximately two-thirds of patients with steroid-dependent CD[5–7] and may achieve and maintain complete or near-complete mucosal healing and histologic remission in a significant proportion of patients with Crohn's colitis, ileocolitis, and severe postoperative recurrent ileitis.[26–30] However, the healing effect of AZA has not been adequately studied in prospective clinical trials.

The aim of this study was to compare the long-term effects of AZA and BUD on the endoscopic and histologic activity of CD in patients with steroid-dependent inflammatory CD who had achieved clinical remission on corticosteroids.

MATERIALS AND METHODS

Patients

Eligible patients were between 18 and 67 years and had luminal (inflammatory) steroid-dependent Crohn's ileocolitis or proximal colitis in remission. Remission was defined as maintenance of a Crohn's Disease Activity Index (CDAI) value of less than 150.[31] Steroid-dependency was defined as at least 1 flare of CD in the previous 6–12 months which was treated effectively with steroids with a relapse of CD during tapering or soon after withdrawal of steroids. The location and extent of CD had been confirmed by ileocolonoscopy, gastroscopy, and a small-bowel enema within 12 months prior to randomization. Patients had a recent flare that was treated with a starting dose of oral prednisolone of 0.75 mg/kg a day that was tapered gradually to the lowest dose that maintained remission effectively for at least 1 month prior to randomization.

Patients were excluded from the study if they were maintained only on mesalazine or reported effective prior treatment with AZA for more than 1 month or had received infliximab. Patients were also excluded if they had left-sided colonic CD, fibrostenotic or fistulizing CD, prior intestinal resection, or inflammatory disease maintained in remission on more than 30 mg prednisolone a day. Additional exclusion criteria were diabetes mellitus, a history of tuberculosis, HBV, HIV, or HCV infection, regular use of nonsteroidal antiinflammatory drugs, existing or intended pregnancy, lactation, peptic ulcer disease, and chronic renal, hepatic, or heart failure.

Study Design

This was a prospective, randomized, controlled, endoscopist- and pathologist-blind study that was conducted between January 1998 and November 2001 in accordance to the Hong Kong revision (1983) of the Declaration of Helsinki. Eligible patients were randomly allocated to AZA or BUD using a computer-based random number generator. Although patients were not blinded as to the intervention they were receiving they were unaware that there was another treatment arm in the study. All patients gave written informed consent. There were separate informed consents for each study medication.

During a 14-day screening period patients underwent clinical assessment, routine hematologic and biochemical tests, calculation of CDAI, and assessment of QOL using the IBDQ.[32] Then patients underwent ileocolonoscopy and ulcerated lesions and all lesions were separately recorded and graded using the CDEIS as described by Mary and Modigliani for French GETAID.[33] All endoscopies were performed by the same physician (G.J.M.) who was unaware of the patient's clinical status and treatment category. Four biopsies were taken from each explored colonic segment (rectum and sigmoid colon, descending colon, transverse colon, cecum, and ascending colon) and the terminal ileum, if entered. Histologic activity of CD was assessed by a single experienced, blinded IBD pathologist (K.P.) as defined by D'Haens et al.[28] An average histology score (AHS) was extracted by dividing the sum of individual intestinal segmental scores by the number of intestinal segments explored.

Patients in remission at the end of the screening period were randomized to generic AZA (2–2.5 mg/kg a day) or 6–9 mg a day controlled-release BUD (Budecol; AstraZeneca A&D, Lund, Sweden). Thiopurine methyltransferase (TPMT) measurements were not performed prior to initiation of AZA. The daily dose of BUD was determined by the level of prednisolone dependency (9 mg for patients maintained in remission on 15–30 mg prednisolone and 6 mg for those maintained on less than 15 mg prednisolone a day). The dose of prednisolone at randomization remained stable for another 4 weeks in both treatment groups and subsequently was tapered off by 5 mg per week.

Patients visited the Outpatient Clinic at 2-month intervals for 1 year or to withdrawal from the study for a relapse of disease, treatment-related adverse events, poor compliance with treatment or study protocol, loss to follow-up, intercurrent illness, or personal choice. Patients unable to completely wean conventional steroids were also withdrawn from the study. At each visit or on the occasion of relapse, clinical assessment, laboratory tests, a check for adverse events and compliance, and CDAI and QOL calculations were performed. Patients were also contacted

regularly by phone calls between visits in order to report on their general condition, any adverse events possibly related to treatment or disease, and the results of laboratory tests. The latter included a full blood count, erythrocyte sedimentation rate (ESR), C-reacting protein (CRP), serum levels of glucose, urea, creatinine, electrolytes, and amylase, liver function tests, prothrombin time, and urinalysis. Tests for eye lens cataract and glaucoma were performed at baseline and at 6 and 12 months. Stool microscopy, parasitology, and cultures were performed during screening and on the occasion of relapse. Fasting morning plasma cortisol levels were measured by radioimmunoassay during screening and at 6 and 12 months.

Ileocolonoscopy with biopsies was performed as previously described at the end of the trial or whenever the trial was prematurely stopped. In addition to CDEIS, any changes in endoscopic appearance compared to baseline endoscopy were classified in 4 categories as described by D'Haens et al[29]: complete mucosal healing, when all pathological findings had disappeared; near-complete healing, when occasional aphthae, residual superficial erosions, or thickened folds were seen; partial healing, when the length of inflamed areas had been shortened but there were still considerable numbers of persisting ulceration and/or cobblestone; and unchanged or worse, when lesions were similar or more severe compared to baseline findings.

Patients who were still in remission at the end of the study entered a 6-month study extension to assess solely maintenance of remission on AZA or BUD. These patients were seen in the outpatient clinic at monthly intervals with clinical evaluation and CDAI calculations.

Efficacy and Safety Assessments

The primary endpoint was the rate of mucosal healing and histologic remission of CD at the end of the study. The primary efficacy analysis was based on patients who completed the study (per protocol) but also on all patients who received at least 1 dose of the study medications (intention to treat, ITT). Secondary endpoints were the annual relapse rate of CD, the time in remission, the time to discontinuation of the study medications, changes in CDAI scores and health-related QOL, and safety of the treatment and were analyzed on an ITT basis.

All adverse events were recorded and graded for their severity as mild, moderate, or severe irrespective of their possible association with the study medication. Compliance with treatment was defined as the consumption of more than 80% of the study medications in the 2-month interval between visits and was assessed by count of the returned pills. Additional medications and reasons for treatment were also recorded. Treatment failure was defined as the withdrawal of a patient from the study irrespective of cause. Relapse was defined as recurrence of symptoms of CD resulting in an increase in CDAI of more than 100 points from baseline and more than 150. CDAI scores 150–219 indicated a mild, 220–450 moderate, and over 450 severe relapse of disease.

Statistical Analysis

In calculating the sample size it was estimated that 39 patients per group would have to be studied to detect a 40% difference in mucosal healing and histologic remission rates with 80% probability (2-sided test; $\alpha = 0.01$), assuming a mucosal healing effect 70% for AZA[15,27–29]. On average, 1 patient was randomized every 20 days for 4 years.

Data are expressed as mean values ± 1 SD or median and range. The normality of the data was examined using the Kolgomorov–Smirnov test. Ninety-five intervals were constructed to express differences in measured parameters. Comparisons between groups were performed by unpaired *t*-test or Mann–Whitney *U*-tests as appropriate. All correlations were calculated according to Pearson's or Spearman's correlation coefficient as appropriate. Chi-square statistics, according to an equidistribution test, were applied to compare the effect of treatment on relapse rates of disease. CDAI and IBD-QOL data were compared using the analysis of variance combined with multiple-range analysis according to Tukey's Honestly Significant Differences (HSD). Multivariate logistic regression analysis was performed to evaluate factor(s) predicting endoscopic mucosal healing, such as age (<40, ≥40 years), gender, smoking (yes/no), duration of disease (<1 year/1–2 years/>2 years), location of disease (ileocolitis/proximal colitis), need for steroids at disease diagnosis (yes/no), need for hospital admission at diagnosis (yes/no), duration of steroid treatment (<6 weeks/>6 weeks), and baseline CDEIS.

To study the effect of treatment on CDAI and IBD-QOL data the last extended value method was used. Kaplan–Meier curves were constructed to depict the time to relapse and/or premature withdrawal from the study. Elaboration of data was accomplished using the Statgraphics Statistical Package (Manugistics, Rockville, MD).[34] *P*-values less than 5% were considered statistically significant.

RESULTS

Patient and Disease Characteristics at Baseline

Of the 77 patients recruited in this study, 37 received AZA and 38 received BUD (Fig. 1). At randomization, there were no significant differences in any patient or disease-related parameters between treatment groups (Table 1), including laboratory tests, CDAI, IBDQ, CDEIS, and AHS.

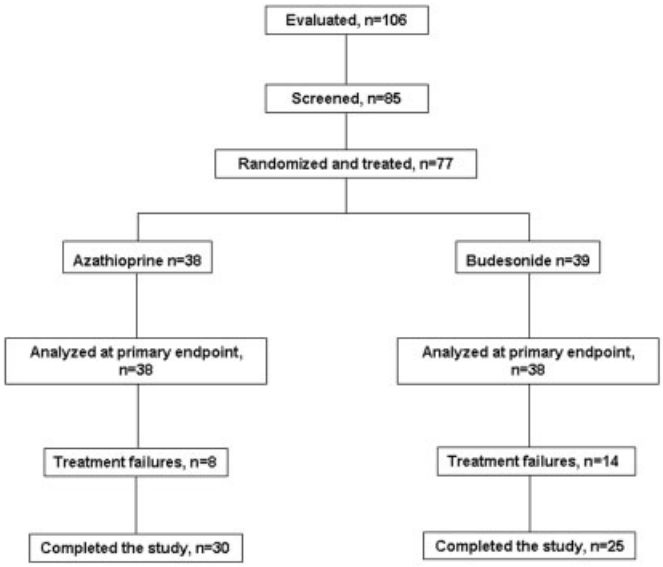

FIGURE 1. Flow chart of patients with steroid-dependent Crohn's ileocolitis or proximal colitis randomized to AZA 2–2.5 mg/kg a day or BUD 6–9 mg a day and reasons for discontinuation.

Mucosal Improvement

At baseline, the mean (SD) of CDEIS score for AZA- and BUD-treated patients were similar (Table 2). At the end of the study significantly more AZA-treated than BUD-treated patients showed mucosal improvement or complete mucosal healing (Table 2). Figure 2 depicts percentages of mucosal improvement in the whole study population. Among those who completed the study, 25 of 30 (83%) AZA-treated patients achieved complete ($n = 22$) or near-complete ($n = 3$) mucosal healing compared with only 6 out of 25 (24%) patients on BUD (chi-square test 17.18, $P = 0.0001$); endoscopic lesions did not change only in 1 AZA-treated compared with 12 BUD-treated patients. Regarding mucosal improvement in the terminal ileum of study completers, complete healing was endoscopically confirmed in 11 of 19 (59%), near-complete healing in 4 of 19 (21%) patients, partial healing in 3 of 16 (16%), and no change in only 1 of AZA-treated patients compared with 2 of 17 (12%), 3 of 17 (18%), 4 of 17 (24%), and 6 of 17 (35%) BUD-treated patients, respectively ($P = 0.001$ and $P = 0.04$, for complete healing and worse/no change, respectively). At baseline the ileocecal valve was entered with difficulty in 8 and 13 patients who received AZA and BUD, respectively. However, at the end of the trial the ileocecal valve was easily intubated in 4 of 8 AZA-treated patients compared with only 4 of 13 BUD-treated patients; in another 2 BUD-treated patients the ileocecal valve was stenosed and the terminal ileum could not be explored. Multivariate logistic regression analysis identified early initiation of AZA during the course of disease (<1 year) as the only factor predicting complete endoscopic healing of CD.

Histologic Improvement

At baseline the AHS was similar for the 2 treatment groups (5.92 ± 1.70 for AZA versus 5.72 ± 1.63 for BUD,

TABLE 1. Patient and Disease Characteristics at Randomization

Parameter	Treatment Group	
	AZA ($n = 38$)	BUD ($n = 39$)
Sex ratio (male/female)	17/21	17/22
Median age (range) (yr)	34.3 (19–59)	34.5 (19–62)
Mean (SD) of body weight (kg)	61.2 (±5.9)	60.8 (±6.1)
Smokers (%)	35 (92%)	36 (92.3%)
Disease location		
Ileocolitis (L_3B_1) %	24 (63%)	26 (67%)
Proximal colitis (L_2B_1) %	14 (37%)	13 (33%)
Mean (SD) of disease duration (yr)	1.8 (0.6)	1.9 (0.7)
Mean (SD) of symptoms onset (yr)	2.1 (0.5)	2.1 (0.6)
Mean (SD) CDAI at entry	132 (15.0)	129 (15.1)
Mean (SD) duration of current attack (mo)	3.1 (0.6)	3.3 (0.4)
Mean (SD) time on steroids (wk)	9.0 (1.2)	9.0 (1.4)
Mean (SD) time in remission (wk)	4.9 (0.8)	5.1 (1.0)
Median (range) dose of steroids at entry (mg)	20 (10–25)	20 (8–25)
Mean (range) of prior treatments with steroids	2 (1–3)	2.2 (1–4)
Extraintestinal manifestations	15	13

TABLE 2. CDEIS Scores Before and After 1-Year Treatment with AZA 2-2.5 mg/kg a Day or BUD 6-9 mg a Day

	Azathioprine		Budesonide		
Treatment Group	PP $n = 30$	ITT $n = 38$	PP $n = 25$	ITT $n = 39$	P
Before treatment	7.00 ± 3.00	7.20 ± 3.10	6.90 ± 3.70	7.10 ± 3.50	1.0
After treatment	0.55 ± 1.60	1.62 ± 2.58	6.51 ± 4.58	7.20 ± 3.20	<0.0001
P	<0.0001	<0.001	0.69	1.0	

CDEIS, Crohn's Disease Endoscopic Index of Severity; PP, per protocol; ITT, intention-to-treat.
Values are expressed as mean ± standard deviation.

mean ± SD, ITT analysis, $P = 0.5$). No significant difference was seen in the AHS in the BUD group between baseline (5.72 ± 1.63) and the end of the study (6.01 ± 1.72, ITT analysis, $P = 0.31$), although the terminal ileum could not be explored in 2 patients. However, the AHS for AZA-treated patients fell significantly at study termination (2.92 ± 1.93, ITT analysis, $P < 0.01$ versus baseline AZA-AHS and versus BUD-AHS at study termination, respectively). Improvement was seen across all acute histologic parameters (epithelial damage, acute lamina propria inflammatory cell infiltrate, erosions and/or ulcers) irrespective of disease location. In addition, the number of biopsies affected was significantly lower in AZA- than BUD-treated patients (32% versus 82%, $P < 0.001$). The only histologic parameters unaffected by AZA were the glandular architecture and the presence (but not the degree) of chronic inflammation. Similar results were obtained when data were analyzed per protocol.

Maintenance of Clinical Remission

Eight patients (21%) in the AZA group, 5 with ileocolitis and 3 with proximal colitis, withdrew because of relapse of CD ($n = 6$) or adverse events ($n = 2$) compared with 14 (36%) patients in the BUD group, 9 with ileocolitis, and 5 with proximal colitis, who withdrew for relapse of disease (Fig. 1; ITT analysis $P = 0.2$). The time to treatment discontinuation was not statistically different between AZA-treated (181 ± 114 days) and BUD-treated patients (123 ± 43 days, 95% confidence interval [CI] −12 to 129 days, $P = 0.1$) but AZA prolonged the period of steroid-free clinical remission compared to BUD (191 ± 106 days versus 123 ± 43 days, respectively [mean ± SD], 95% CI −1 to 136 days, $P = 0.054$). Furthermore, the median (range) CRP and ESR levels in the AZA group were significantly lower than in the BUD group (0.4 [0.1–5.4] mg/dL and 13 [3–35] mm/h versus 2.4 [0.4–24.5] mg/dL and 35 [13–75] mm/h, respectively, ITT analysis, $P < 0.0001$). Figure 3 depicts the probability of remaining disease-free during treatment.

Four of 9 patients receiving 9 mg BUD a day compared with 10 of 30 patients receiving 6 mg BUD a day relapsed. The level of prednisolone-dependence in these 2

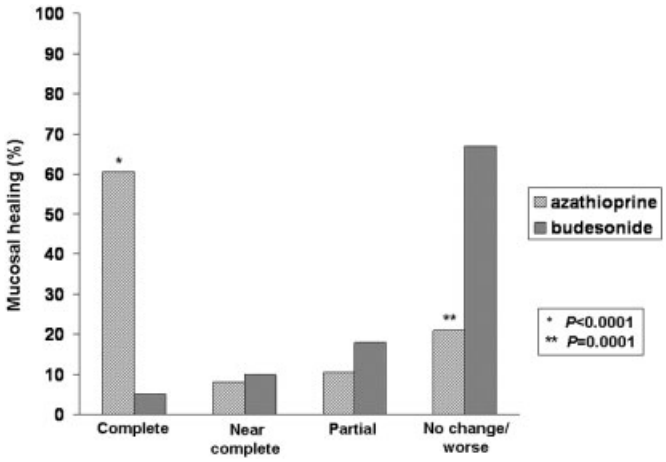

FIGURE 2. Rates of mucosal healing in patients treated with at least 1 dose of AZA (2–2.5 mg/kg a day) or BUD (6–9 mg/day) (ITT analysis).

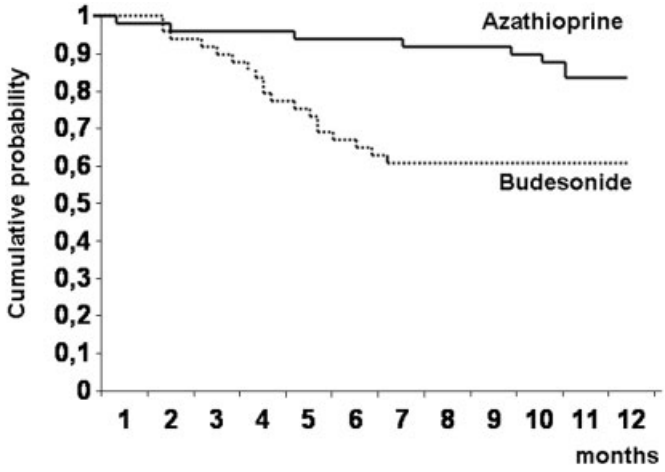

FIGURE 3. Cumulative probability of maintaining remission of Crohn's ileocolitis or proximal colitis during the 1-year treatment with AZA 2–2.5 mg/kg a day or BUD 6–9 mg a day (ITT analysis, log-rank test: 2.71; $P > 0.05$).

groups ranged from 15–25 mg and 8–15 mg prednisolone a day, respectively ($P = 0.065$).

After a further 6-month treatment extension, 1 patient in the AZA group and 7 in the BUD group relapsed; thus, after 18 months remission rates were significant in favor of AZA (76% versus 36%, respectively, $P = 0.03$; log-rank test 9.07, $P < 0.005$).

Adverse Events

No lethal adverse events were observed but numerically more adverse events were recorded in the AZA ($n = 112$) than in the BUD group ($n = 83$). Two AZA-treated patients were withdrawn for pancreatitis and severe, reversible leukopenia, respectively. Twenty-five patients on AZA and 14 on BUD developed infections, mainly from the upper respiratory tract; 1 patient on AZA suffered a herpes zoster infection. Transient abdominal pain and/or diarrhea developed in 23 AZA-treated and 17 BUD-treated patients. Other AZA-related adverse events were transient paresthesias (2), hair loss (1), and elevated transaminases (1). BUD-related adverse events were mild acne (1), moon face (5), and transient hair loss (1). White blood cell counts and platelet counts were significantly lower in the AZA than in the BUD group (4.330 [0.650] versus 8.950 [1.550], mean [SD], $P < 0.0001$, respectively; and 285.000 [15.000] versus 300.000 [9.000], mean [SD], $P < 0.01$, respectively). In the BUD group cortisol levels were lower at the end of the study compared to baseline but were still within the normal range; no increased serum glucose levels were recorded. Cases of eye lens cataract were not identified in the BUD group. There was no deterioration in the bone mineral density scores in 12 patients tested before and after treatment with BUD.

DISCUSSION

In this study the comparative efficacy of AZA and BUD on mucosal healing, histologic remission, and maintenance of clinical remission were studied in patients with steroid-dependent inflammatory Crohn's ileocolitis or proximal colitis who had achieved clinical remission on conventional steroids. At the end of the 1-year follow-up, numerically more patients on AZA than BUD maintained clinical remission of CD without conventional steroids; this difference reached statistical significance in the 6-month poststudy treatment-extension period. This clinical effect of AZA was associated with a highly significant rate of complete or near-complete mucosal healing. Mucosal healing in AZA-treated patients was associated with a significant reduction in the histologic activity of CD, although complete histologic remission was not achieved. In contrast, although almost 64% of BUD-treated patients were still in clinical remission at the end of the study, the healing effect of BUD was disappointing compared with historical controls treated with conventional steroids.[15] Furthermore, BUD did not improve the histologic activity of CD.

The healing effects of AZA have been documented in case-series of patients with Crohn's colitis or ileocolitis. In an open-label trial, Sandborn et al[26] reported that a loading dose of intravenous AZA induced endoscopic healing in 3 of 6 patients with severe postoperative recurrent ileitis. Using endoscopy or radiology, the Leuven group evaluated macroscopic healing of lesions in the neoterminal ileum in 15 of 19 patients with severe postoperative recurrence of CD who had achieved clinical remission on steroids and AZA (2 mg/kg/day) but had weaned completely from steroids at least 6 months prior to investigation.[27] AZA achieved complete healing in 6 of 15 patients, near-complete healing in 5 of 15 patients, partial healing in 3 of 15 patients, and only 1 patient had unchanged lesions. Two years later, the same group retrospectively compared the endoscopic and histologic findings before and after treatment with AZA in 20 consecutive patients with Crohn's colitis and ileocolitis.[29] Patients were receiving AZA for 24.4 ± 13.7 months and had weaned steroids for at least 3 months. Complete healing was observed in 14 (70%), near-complete healing in 2 (10%), partial healing in 3 (15%), and no healing in 1 of 20 (5%) patients. In the terminal ileum, complete healing was seen in 7 (54%), near-complete healing in 2 (15%), partial healing in 1 (8%), and no healing in 2 of 13 (15%) patients. Histology revealed disappearance of acute inflammatory infiltrate, although architectural disturbance did not improve. In an AZA withdrawal study Lemann et al[30] reported that 45 patients who were treated with AZA for at least 42 months had low CDEIS values and 16 of 45 (36%) had complete mucosal healing (CDEIS = 0). The presence of endoscopic lesions or ulcerated areas was not predictive of relapse of CD in patients who discontinued AZA. It has been argued by Cosnes et al[35] that despite increased use of AZA between 1978 and 2002 the cumulative risk for intestinal resection for complicated CD has remained unchanged. Even so, a small minority of patients (16 of 190, 8.4%) in this French cohort came to surgery and this was probably due to the introduction of AZA rather late in the course of CD.[36]

Our prospective, controlled study is strikingly similar to a retrospective case-series of CD patients treated with AZA in Leuven.[27,29] In those studies patients achieved a high degree of mucosal healing on AZA and only lesions in the vicinity of the ileocecal valve persisted. Endoscopic healing was accompanied by a dramatic improvement in certain histologic parameters and especially acute cellular infiltration and epithelial damage, maintenance of clinical remission, and normal inflammatory indices, including serum CRP, ESR, and platelet counts. In

contrast, chronic inflammation and architectural changes took much longer to remit. The high rate of mucosal healing observed in our study may be due to initiation of treatment early after the onset of symptoms of CD in patients who were AZA-naïve. Recent reports have shown that combination treatment with anti-TNF agents and AZA or anti-TNF monotherapy offered early in the course of CD may induce and maintain high rates of clinical remission and mucosal healing.[37,38] Furthermore, baseline endoscopic evaluation was performed in patients who had already achieved clinical remission and perhaps a certain degree of mucosal healing on prednisolone. The healing effect of AZA was similarly equal in the terminal ileum and the proximal colon. In contrast, any healing effect of BUD was only seen in the proximal colon.

In conclusion, this study suggests that the early administration of AZA may be very effective not only in maintaining clinical remission but also in inducing much higher rates of mucosal healing and histologic remission than BUD in patients with steroid-dependent inflammatory (luminal) Crohn's ileocolitis or proximal colitis of recent onset who have achieved clinical remission on corticosteroids. These effects are associated with an excellent quality of life.

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